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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/801,956	FUJIMOTO ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *4,9,20,38,48,62 and 71-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10-19,21-28,30-37,39-47,49-61,63-70 and 74-80* is/are rejected.

7)☒ Claim(s) *1 and 65* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/1/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I, claims 1-3, 5-8,10-19, 21-28, 30-37, 39-47, 49-61, 63-70, 74-80 in the reply filed on 8/17/2006 is acknowledged. The traversal is on the ground(s) that that searching all four recited markers would encompass all possible combinations. This is not found persuasive because searching for the combination of all four markers would not necessarily produce art on a combination of 3 markers, such as D12S393, D12S1706, and D12S346. Likewise searching for subcombination: D12S393, D12S1706, and D12S346 would not necessarily result in finding art on subcombination: D12S1657, D12S393, D12S1706 and vice versa. As searching for all four recited together markers would not necessarily result in finding art on specific subcombinations of the four recited markers, searching for subcombinations of the specific combination of markers would result on a burden of search for the office.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 4, 9, 20, 38, 48, 62, 71-73 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/17/2006.

A first action on the merits of claims 1-3, 5-8, 10-19, 21-28, 30-37, 39-47, 49-61, 63-70, and 74-80 follows.

Priority

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/455006, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Claims 3, 8,19,28,37,46, 60, are drawn to the sample being plasma, however '006 does not teach the use of plasma. Claims 14, 23, 32, 41, and 68 drawn to colon cancer, claims 15, 24, 33, 42, 69 drawn to breast cancer and claims 16, 25, 34, 43, 70 drawn to brain cancer are not taught in '006. Further claims 26-34 are drawn to the use of 12q22-23 markers for indicating progression of cancer, the '006 specification teaches a correlation of 12q22-23 markers with survivability, but not cancer progression (see 1st full paragraph page 6). Claims 52 and 53 are drawn to RLM and ITM melanoma, which is not taught by '006 specification.

Claim Objections

1. Claims 1 and 65 objected to because of the following informalities:

Claim 1 recites "comprisingproviding". This should be corrected to "comprising providing".

Claim 65 recites "matastatic", and should be corrected to "metastatic".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 5-8, 10-19, 21-28, 30-37, 39-47, 49-61, 63-70, and 74-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting melanoma in a human subject comprising detecting the combination of D12S1657, D12S393, D12S1706, and D12S346 markers in the 12q22-23 region in plasma or serum samples wherein the presence of the combination is indicative of incidence and progression of melanoma occurrence, does not reasonably provide enablement for "any" marker of 12q22-23 in "any" cancer in "any" subject. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to methods of detecting "any" DNA marker or "any" combination of markers in the 12q22-23 in "any" subject. The claims are further drawn to the LOH of "any" 12q22-23 marker or "any" combination of 12q22-23 markers in "any" subject and "any" subject with cancer. The claims are further drawn to melanoma, colon cancer, brain cancer and breast cancer.

The amount of direction or guidance and the Presence and absence of working examples in the specification.

The specification teaches there is an unexpected LOH of markers for 12q22-23 (see page 3, lines 5-8). The specification further teaches that the 12q22-23 region encompasses the APAF-1 locus (see page 9, line 26) and there was a statistically significant allelic imbalance in metastatic tumors and primary melanoma ($p=0.02$)(see page 9, lines 28-29). Further APAF-1 loss was significantly correlated with a worse prognosis ($p<0.05$) (see page 10, 1st line). The specification further teaches melanoma

patients that responded to chemotherapy had a significantly lower frequency of allelic imbalance at 12q22-23 (P<0.029) and better prognosis (p<0.046) (see page 10 line 12-13), then patients with an allelic imbalance. Further the specification teaches the use of 12q22-23 markers: D12S1657, D12S393, D12S1706, and D12S346.

The specification teaches LOH frequencies in primary melanomas were 20%, 31%, 13% and 17% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification teaches LOH frequencies in metastatic melanomas were 23%, 35%, 17% and 21% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification asserts that there is a higher frequency of allelic imbalance in metastatic melanoma than primary melanoma (P=0.02), although there is no frequency differences between stage III melanoma and stage IV melanoma (see page 24,line 11 to page 15 line 1). The specification further teaches there is no correlation between APAF-1 status and overall survival in primary melanoma, but there is a statistically significant correlation between APAF-1 status and Stage III/IV melanoma (p=0.05) (see page 26, lines 10-15). Further survival of stage III metastic melanoma and stage III metastatic melanoma with RLM was statistically correlated with APAF-1 status (P=0.03, p=0.02) but metastatic melanoma with ILM was not (p=0.17) (see page 26 line 25-page 26 line 3). It thus appears that LOH of D12S1657, D12S393, D12S1706, and D12S346 is correlated with survival of patients with stage III metastatic melanoma with RLM, but not survival with stage III metastatic melanoma with ILM. The specification is silent on LOH of D12S1657, D12S393, D12S1706, and D12S346 and stage IV melanoma.

Further the specification teaches the effect of allelic 12q22-23 in serum samples on melanoma patient outcomes. The specification teaches a significant relationship of D12S1657, D12S393, D12S1706, and D12S346 markers (p=0.029) before chemotherapy in the responder group, but not in the responder group after chemotherapy (see page 36, line 11-15). It thus appears that chemotherapy results in LOH for D12S1657, D12S393, D12S1706, and D12S346 markers in melanoma. Further patients with D12S1657, D12S393, D12S1706, and D12S346 LOH had a statistically significantly worse survival rate (p=0.046) (see page 36, line 17) and response to chemotherapy was related to survival (p<0.001) (see page 36, line18).

The specification further teaches in tables 6, D12S1657, D12S393, D12S1706, and D12S346 LOH occur in no colon adenomas, 21% of primary colon cancers, or 54% of colon cancer derived liver metastases. Further the specification teaches in table 7, there are a D12S1657, D12S393, D12S1706, and D12S346 LOH in 25% of primary breast cancers. However the specification does not teach that the D12S1657, D12S393, D12S1706, and D12S346 LOH are statistically correlated with colon cancer or breast cancer. The specification does not teach any studies of D12S1657, D12S393, D12S1706, and D12S346 markers and brain cancer.

The specification does not teach any markers other then D12S1657, D12S393, D12S1706, and D12S346 to the 12q22-23 region. The specification does not teach the presence of the 12q22-23 region in any non-human species, or a correlation of this 12q22-23 region to cancer in any species other than human. The specification does not teach a statistically significant relationship between any cancer other then melanoma

and 12q22-23 LOH. The specification does not even address brain cancer and 12q22-23 or teach a statistical relationship between LOH of D12S1657, D12S393, D12S1706, and D12S346 and breast or colon cancer. The specification does not teach that the markers for 12q22-23 are markers of APAF-1.

The specification does teach a statistically significant association of 12q22-23 LOH and melanoma, therapeutic response and outcome, but the specification teaches there is not a statistically significant relationship after chemotherapy, making the marker unpredictable for melanoma in those cases.

The specification does teach D12S1657, D12S393, D12S1706, and D12S346 are associated with melanoma and its progression and outcome. The specification teaches that the recited markers are associated with melanoma and response, before but not after chemotherapy. The specification further teaches the recited markers correlate with survival of type III melanoma with RLM, but not ILM. The specification teaches only D12S1657, D12S393, D12S1706, and D12S346 markers of 12q22-23. The specification does not teach a statistical relationship of recited markers with a cancer other then melanoma in subjects other than humans.

The state of prior art and the predictability or unpredictability of the art:

The prior art teaches that LOH 12q22-23 is common in metastatic melanoma (see abstract, Soegnas, et al Nature, 2001, vol 409, 207-211). The prior art teaches 12q22-23 LOH is indicative of poor response to chemotherapy, (see page 209, column 1, lines 8-10). The prior art does not teach a correlation between 12q22-23 LOH and any cancer other than melanoma.

The prior art does not teach 12q22-23 LOH is associated with "any" cancer other then melanoma. Soegnas teaches 12q22-23 marker, D12S327 (figure 1b), which the specification teaches does not teach but is encompassed by the claims. Further, Geneloc lists numerous other 12q22 markers that are encompassed by the claims, but are not taught in the specification. (see geneloc, bioinfo.weizmann.ac.il/cgi.bin/genloc/display_map.pl, pages 1-14).

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Further the prior art does not teach LOH 12q22-23 exists in any other species then human. It does not teach LOH 12q22-23 is functional representative of any other chromosome in any other species.

Further the claims are drawn to the association of "any" cancer with LOH of "any" 12q22-23 marker. Any cancer includes leukemia, bone, lung, bladder, endometrial, cervical, thyroid, prostate, and lymphoma. The prior art and the specification are silent on 12q22-23 LOH and "any " of these cancers.

As the prior art does not teach 12q22-23 region is associated with "any" cancer in "any" subject in "any" species it would be unpredictable to associate LOH for 12q22-23 with "any" cancer.

The level of skill in the art:

The level of skill in the art is deemed to be high

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish that a predicative relationship exists between LOH of "any"12q22-23 marker and "any" cancer in "any" subject of "any" species. Experimentation would be replete with unpredictable trial and error analysis because the specification does not teach LOH of "any" 12q22-23 marker is associated with "any" cancer in "any" species, however the specification does teach melanoma is associated with the loss of D12S1657, D12S393, D12S1706, and D12S346. However, the specification teaches that the recited markers are lost following chemotherapy and are not predictive of survival in type III melanoma with ILM. As these markers are lost with chemotherapy and are not predictive of survival with type III melanoma with ILM they are not predictable markers for "any" cancer in "any" subject, or even "any" melanoma. The art confirms melanoma is associated with LOH of markers: D12S1657, D12S393, D12S1706, and D12S346 , but

one of skill in the art would have to recruit an enormous population of ethnically diverse subjects and species with "any" cancer and cancer-free controls and determine the association of loss of "any" 12q22-23 marker with "any" cancer to determine a predictive relationship between "any" cancer and loss of "any" 12q22-23 marker.

Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation to first determine a predictive relationship between loss of "any" 12q22-23 marker with "any" cancer to determine a predictive relationship between "any" cancer and loss of "any" 12q22-23 marker.

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

4. Claims 1-3, 5-8, 10-19, 21-28, 30-37, 39-47, 49-61, 63-70, and 74-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 1,6, 17, 26, 35, 44, and 58 are drawn detecting "any" markers of 12q22-23 in "any" subject in "any" species. Claims 6-8, 10-19, 21-28, 30-

37, 39-47, 49-61, 63-70, and 74-80 are drawn to LOH of 12q22-23 for cancer detection and analysis. Claims 14, 23, 32, 41, and 68 draw the claims to colon cancer. Claims 15, 24, 33, 42, 69 draw the claims to breast cancer. Claims 16, 25, 34, 43, 70 draw the claims to brain cancer. Claims 74, 75,76, 77, 78, and 80 limits the markers to those recited. The claims do not set forth any structural requirements or limitations for "any" subject or "any" species. The claims set forth structural limitation that loss of markers to 12q22-23 region be associated with cancer.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules and their combinations. The specification teaches markers: D12S1657, D12S393, D12S1706, and D12S346. The specification teaches loss of D12S1657, D12S393, D12S1706, and D12S346 is correlated with decreased APAF-1 expression. The specification does not teach any other marker in the recited region. The specification does not teach that the structure of 12q22-23 region is conserved across species.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed by complete structure. The instant specification teaches12q22-23 makers: D12S1657, D12S393, D12S1706, and D12S346. The species described in the specification is not representative of the genus of nucleotides encompassed by "any" 12q22-23 marker.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and

functional attributes that would distinguish different members of the claimed genus. While the claims and specification disclose an association of melanoma with the recited 12q22-23 markers such a functional limitation cannot be considered as a distinguishing feature because the 12q22-23 region encompasses an enormous number of nucleotides and markers that are not attributed to melanoma. The skilled artisan would not be able to ascertain a structure/function relationship between recited markers and "any" 12q22-23 markers in such a way as to predictably associate other 12q22-23 markers with any cancer. The claims read in light of the specification encompass any nucleic acid molecule capable of being a marker of the 12q22-23 region. This region encompasses millions of bases. Markers for 12q22-23 would thus encompass any combination of nucleotides that would hybridize to 12q22-23, from 10 nucleotides to the full length of the 12q22-23 region. Thus "any" marker of the 12q22-23 region encompasses 100's of millions of nucleotide sequences. Further the claims encompass "any" subject and "any" cancer. The specification only teaches a statistical correlation of the recited markers with melanoma in humans. Melanoma is not representative of "any" cancer, which includes: leukemia, bone, lung, bladder, endometrial, cervical, thyroid, prostate, and lymphoma. Further humans are not representative of "any" subject, such as dog, cat, mouse, etc.

In the instant application, the provided information regarding nucleic acid "any" marker of 12q22-23, does not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed 12q22-23 markers.

Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding "any" 12q22-23 marker is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules encompassed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims, except 12q22-23 markers: D12S1657, D12S393, D12S1706, and D12S346.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 74-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to the restriction response applicant elected all markers recited, and canceled all previous claims directed to possible combinations or subcombinations. Applicant added by amendment claims 74-80, which recite "any" combination of markers recited. It is unclear if the combination is one, two, three, or four markers. The metes and bounds of the claims are unclear in view of the restriction response.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1,5, 6, 10, 11, 12, 13, 17, 21, 22, 26, 30, 31, 35, 39, 40, 58, 59, 63, 64, 74-78 and 80 are rejected under 35 U.S.C. 102(b) as being anticipated by Soengas, et al (Nature, 2001, volume 409, pages 207-211).

As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, steps of independent claims 1, 6, 17, 26, 35, and 58 are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of the preamble to claims 1, 6, 17, 26, 35, and 58 merely sets forth the intended use or purpose of the claimed methods, but does not limit the scope of the claims.

As the specification does not specifically state a definition of acellular DNA, acellular DNA is given its broadest reasonable interpretation of any DNA not contained in a cell, including DNA isolated from a cell, tumor, etc.

With regards to claim 1, Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatelite markers (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. This is being interpreted as isolating genomic DNA , thus making it acellular.

With regards to claim 5, Soegnas teaches the use of markers encompassing the APAF-1 locus (see page 207, 2nd column, lines 17-19).

With regards to claim 6, 11, 13, Soegnas teaches loss of APAF1 and micro satellite markers in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. This is being interpreted as isolating genomic DNA , thus making it acellular. Soengas teaches detecting cancer by LOH of markers to 12q2-23.

With regards to claim 10, 30, 63, Soegnas teaches the use of markers encompassing the APAF-1 locus (see page 207, 2nd column, lines 17-19).

With regards to claim 12, Soegnas teaches detection of APAF-1 in primary melanoma cells.

With regards to claims 17, 21, and 22, Soegnas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in

primary melanoma (see page 208, 1st column, line 1). Soegans thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

With regards to claim 26, Soegnas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

With regards to claim 31, Seognas teaches melanoma (see page 208, lines 2-4).

With regards to claims 35,39, 40, Soegnas teaches there is correlation of APAF-1 levels and response to adriamycin in melanoma cells(see page 209, column 1, lines 8-10). Soegans teaches that APAF-1 levels are lower in melanoma's due to APAF-1 LOH. Soegnas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

With regards to claim 58, Soegnas teaches assessment of APAF1 status improves therapeutic management for patients, as it is a required for apoptosis and thus a marker of chemosensitivity (see page 210, 2nd column, lines 20-26).

With regards to claim 59, Soegnas teaches LOH analysis from tumor samples (see page 210, 2nd column, analysis of APAF-1 locus).

With regards to claim 64 and 65, Soegnas teaches melanoma and metastatic melanoma (see abstract; page 207 2nd column, lines12-14).

With regards to claims 74, 75,76, 77, 78, and 80, Soegnas teaches markers recited (see figure 1B).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-3, 5, 6-8, 10, 11, 12, 13, 17-19, 21, 22, 26-28, 30, 31, 35-37, 39, 40, 58, 59-61, 63, 64, 74-78 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al (US Patent 6156504).

As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, steps of independent claims 1, 6, 17, 26, 35, and 58 are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of the preamble to claims 1, 6, 17, 26, 35, and 58 merely sets forth the

intended use or purpose of the claimed methods, but does not limit the scope of the claims.

11.

As the specification does not specifically state a definition of acellular DNA, acellular DNA is given its broadest reasonable interpretation of any DNA not contained in a cell, including DNA isolated from a cell, tumor, etc.

With regards to claim 1, Soengas et al teaches detection of lose of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatelite markers (see figure 1 and legend). Seongas further teaches genomic DNA for tumour and normal cells were amplified by PCR. This is being interpreted as isolating genomic DNA , thus making it acellular.

With regards to claim 6, Soegnas teaches loss of APAF1 and microsatellite markers in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumour and normal cells were amplified by PCR. This is being interpreted as isolating genomic DNA , thus making it acellular. Soengas teaches detecting cancer by LOH of markers to 12q2-23.

With regards to claim 17, Soegnas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soegans thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

With regards to claim 26, Soegnas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

With regards to claims 35,39, 40, Soegnas teaches there is correlation of APAF-1 levels and response to adriamycin in melanoma cells(see page 209, column 1, lines 8-10). Soegans teaches that APAF-1 levels are lower in melanoma's with APAF-1 LOH. Soegnas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

With regards to claim 58, Soegnas teaches assessment of APAF1 status improves therapeutic management for patients, as it is a required for apoptosis and thus a marker of chemosensitivity (see page 210, 2nd column, lines 20-26).

Soegnas does not teach the use of plasma (claims 3,8, 19, 28, 61) or serum (2, 7, 18, 27, 60) as a sample.

However, Gocke et al teaches the use of serum (2, 7, 19, 27,37, 60) or plasma (claims 3,8, 18, 28, 36, 61) (see title, abstract). Gocke teaches plasma or serum is easily accessible and amenable for DNA amplification (see column 2, lines 54-55). Gocke further teaches detection colon cancer (claims 14, 32,68), breast cancer (claims 15,33, 69) or brain cancer (claims 16, 34, 70) by this method (see column 30, line 55-58). Gocke teaches use of plasma or serum allow rapid and timely extraction and sensitive detection of extracellular tumor associated or extracellular mutated oncogenic DNA (see column 3, lines 60-63).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soegnas method of detecting 12q22-23

mutations by use of plasma or serum as taught by Gocke, because Gocke teaches plasma or serum is easily accessible and amenable for DNA amplification. The ordinary artisan would be motivated to improve Soegnas method of detecting 12q22-23 mutations by use of plasma or serum as taught by Gocke, because Gocke teaches plasma or serum is easily accessible and amenable for DNA amplification. The ordinary artisan would further be motivated because, Gocke teaches use of plasma or serum allow rapid and timely extraction and sensitive detection of extracellular tumor associated or extracellular mutated oncogenic DNA. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1, 6, 17, 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7, 9, 11, 17, and 23 of copending Application No. 10/809956. Although the conflicting claims are not identical, they are not patentably distinct from each other because although not identical, they are co-extensive in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 of instant invention is drawn to detecting any markers of 12q22-23 from an accellular sample. Claim 1 and 17 of '956 are drawn to detecting markers from an accellular sample.

Claim 6 of instant application is drawn to detection of LOH. Claim 7 of '956 is drawn to detection of LOH.

Claim 17 of instant application is drawn to staging cancer by LOH detection. Claim 9 and 20 of '956 are drawn to staging cancer by LOH.

Claim 26 of instant application is drawn to prognosing cancer by LOH. Claim 11 and 23 are drawn to prognosing cancer by LOH.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

SUPERVISORY PATENT EXAMINER
RAM R. SHUKLA, PH.D.